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Effect of Tobacco Abuse on Long Term Secondary Patency of Arterio-Venous Fistula

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Abstract: **Creation of a functioning arterio venous access accounts for a majority of the inpatient admission in nephrology blocks. Elderly women, diabetics and patients with recent or past history of smoking pose a significant hurdle in creating a successful fistula especially contributing for a large majority of failed fistulas.**
Materials and methods: A prospective study was carried out to evaluate the association of smoking on failed fistulas in patients of end stage renal disease on 60 consecutive patients of end stage renal disease with failed primary vascular access between 14 to 70 years of age over a period of 2 years. Details such as history of diabetes, hypertension, and use of tobacco in any form, prior vascular access surgery and patency of the access are collected.
Results: On multivariate logistic regression analysis using SPSS 15 software, we found that tobacco abuse is associated with failed arterio venous fistula (p value= 0.023).However , partial thrombosis of a failing Arterio venous access , uncorrected, is invariably associated with non-functioning of AV fistula(p value < 0.001)
Discussion: *Ozdemira et al* have concluded that when fistula location was excluded from the analysis, smoking (RR = 4.140, P < .01) was an independent risk factors for thrombosis. *Wetzig et al* have also confirmed that there was a significantly higher incidence of early and late fistula failure in those patients who were cigarette smokers.
Conclusion: Smoking or tobacco abuse is adversely associated with outcome in management of failed fistulas.

Keywords: **Arterio Venous fistula, Smoking, tobacco abuse, Thrombosis of arterio venous access.**

1. INTRODUCTION

Renal replacement therapy is a term used to encompass life-supporting treatments for renal failure. This includes hemodialysis, peritoneal dialysis, hemofiltration, and renal transplantation. The surgeons have continuously faced the challenge of designing the "ideal access" for hemodialysis on a long term basis. During the last two decades, native Arterio venous fistula has evolved as the preferred access as per KDOQI guidelines and the initiatives of Fistula first organization [1,2]. .General international consensus is that the Arterio venous fistula is the "gold standard" once maturity has developed. Surveillance of the functioning Arterio venous access and intervention as and when necessary has been pivotal for haemodialysis.

The Vascular Access Work Group of the National Kidney Foundation (NKF) has concluded that quality of life and overall outcomes for hemodialysis patients could be improved significantly by achieving two primary goals: (1) increase the placement of autogenous arteriovenous (AV) fistulae; and (2) detecting access dysfunction prior to access failure.[2,3] It has been suggested that the order of access preference is radio-cephalic fistula, followed by brachio-cephalic fistula.[2,3]

Missed dialysis is not only responsible for the morbidity but also implicated in accelerated mortality.Failing fistulas need urgent attention to rescue the patency. Due to lack of standardized vascular access surveillance program or protocol, we receive the patients with failed access for hemodialysis. The patients often need to have their dialysis postponed or rescheduled, or they may have to undergo emergency placement of temporary central venous dialysis catheter to obtain the access for dialysis until the fistula can be repaired or a new access created. This accounts for the major cause of re-hospitalization of patients of chronic kidney disease, having emotional, social, and financial implications.

It was our impression that a high proportion of those patients requiring new or revised fistulas were having tobacco abuse. We therefore investigated the patients undergoing haemodialysis with tobacco abuse and related our findings to the long term patency of their arteriovenous fistulas.

Aim and Objectives:

a) To evaluate the different modalities of surgical procedures in the treatment of failed vascular accesses for hemodialysis.

b) To evaluate the effects of Smoking or tobacco abuse on long term secondary patency of the Arterio venous fistula.

2. MATERIALS AND METHODS

A prospective study was carried out on 60 patients of end stage renal disease with failed primary vascular access between 14 to 70 years of age. Children below 14 years of age, patients with adverse cardio respiratory conditions unsuitable for anesthesia, and the patients of peripheral vascular disease are excluded from the study. Details such as history of diabetes, hypertension, and use of tobacco in any form, significant illness, onset of renal disease, type of renal replacement therapy, prior vascular access surgery, and duration of the prior access patency are collected. The patients are evaluated by clinical examination followed by duplex scan of the arterial and venous system of the selected extremity. The procedures are performed under local / regional or general anesthesia. For secondary AVF creation, standard recommended methods are adopted giving priority to the autogenous fistulas. The patients are followed for a minimum of 6 months at monthly intervals for evaluation of the access patency and the complications.

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups. 95% Confidence Interval has been computed to find the significant features. Confidence Interval with lower limit more than 50% was associated with statistical significance.

3. RESULTS

The age and gender distribution of the patients of end stage renal disease show a male preponderance with mean age of presentation to be around 46 years. The left radio cephalic fistula was the preferred primary access procedure for the surgeons providing the vascular access for the purpose of hemodialysis (73.3%). Left brachio cephalic AV Fistula is the second preferred vascular access procedure.

Surprisingly, 40 out of 60 patients of failed AV access were found to be non-diabetic(66.7%). Of the 20 diabetic patients, 3 were on oral hypoglycemic drugs, and 17 were on insulin .Patients well controlled on antihypertensive drugs were taken for the secondary AV access procedure. 27 patients were on single antihypertensive drugs and 20 were on two antihypertensive drugs for the control of hypertension.

40 out of 60 patients were not using tobacco in any form 10 years before the procedure. None of the patients were smoking at the time of creation of the secondary AV access procedure. Taking 100 cigarettes in any period of time is considered to have “ever smoked”. A Pack year is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. One pack year equals 365 packs of cigarettes.(Table 1)

Table 1:Distribution of Patients of renal failure on dialysis and access failure with smoking

Smoking	Number of patients (n=60)	%
None for the last 10 years	40	66.7
None , but smoked in the last 10 years	16	26.7
Current, including the abstinence less than 1 year, <1 pack /day	4	6.7
Current, >1 pack per day	0	0.0

We had 9 cases of postoperative thrombosis of the AV access. Thrombectomy was successful for one of the two patients, 3 patients required revision, and 5 patients had loss of the AV access on account of unfavourable anatomy unsuitable for any intervention. On evaluation of the prior access use we found non-functional access since the creation in 26 out of 60 patients (43.3%), less than six months in 20 out of 60 patients (33.3%), less than one year in 11 out of 60 patients (18.3%).

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Table 2: Secondary procedure for patients of Renal failure on dialysis with access failure and the clinical outcome

Secondary procedure	Number of patients		Function	
	No	%	Present	%
LBC	30	50.0	26	86.7
RRC	14	23.3	12	85.7
RBC	9	15.0	8	88.9
THROMBECTOMY	2	3.3	1	50.0
LT BRACHIO AXILLARY GRAFT	2	3.3	2	100.0
CLOSURE OF AVF	2	3.3	0	0.0
RT ULNO BASILIC AVF	1	1.7	1	100.0
Total	60	100.0	50	83.3
Inference	Functioning is positively associated with all secondary procedure except Thrombectomy and Closure of AVF with P=0.177			

On individual secondary procedure related functional analysis we found LBC (86.7%), RRC (85.7%), and RBC (88.7%) to function satisfactorily .Creating an AV fistula proximally in a suitable site considering clinical and imaging findings can provide an equivalent unassisted patency of the AV fistula. . Thrombectomy was successful in one out of 2 patients attempted (50%). Left Brachio axillary graft and Ulno-basilic AVF was successful in 3 out of 3 cases (100%). However statistical significance cannot be drawn of these 3 results. The functioning of LBC, RRC, and RBC is positively associated (p value= 0.177) .Out of the 10 non functional fistula, technical difficulties in the form of discrepancies in duplex scan reporting and intraoperative findings accounted for a majority of the cases. (Table 2)

Table 3: Correlation of Risk factors with Functioning or non-function of AV access at first follow up using Multivariate logistic regression analysis

Risk factors	Outcome		Univariate Analysis		
	Functioning (n=50)	Non-Functioning (n=10)	OR	95%CI	P value
1.Age >50 years	23(46.0%)	5(50.0%)	1.17	0.3-4.6	NS
2.Male	40(80.0%)	8(80.0%)	1.00	0.2-5.5	NS
3.Multiple Primary access failure	6(12.0%)	2(20.0%)	1.83	0.3-10.7	0.610
4.DM	17(34.0%)	3(30.0%)	0.83	0.2-3.6	NS
5.Hypertension	49(98.0%)	10(20.0%)	-	-	NS
6.Smoking/Tobaco	20(40.0%)	0	-	-	0.023*

On multivariate logistic regression analysis we found smoking/tobacco not to be associated with functioning of AVF(p value= 0.023).However thrombosis of AV access ,uncorrected is associated with non-functioning of AV fistula(p value < 0.001) .Age though is associated with increased atherosclerotic changes with calcific blood vessels were found to be non-associated with decreased functionality of AVF. Males predominating the secondary procedure have 80% functional vascular access. 17 out of 50 patients had diabetes with functional vascular access (34%).Majority of hypertensive patients had functional vascular access (98.0%) which is statistically insignificant. 20 out of 50 patients had history of smoking in the last 10 years. The functional outcome and tobacco smoking was found to be statistically significant with a p value of 0.023. Cephalic vein evaluation on clinical basis was disappointing to assess the functionality of AV fistula(Table 3)

Table 4: Correlation of Risk factors with Functioning of fistula at 6 months follow up using Multivariate logistic regression analysis

Risk factors	Outcome		Univariate Analysis		
	Non-Functioning (n=21)	Functioning (n=39)	OR	95%CI	P value
1.Age >50 years	10(47.6%)	18(46.2%)	0.48	0.10-2.27	0.356
2.Male	14(66.7%)	34(87.2%)	2.76	0.54-14.27	0.225
3.Multiple Primary access failure	4(19%)	4(10.3%)	0.22	0.03-1.61	0.135
4.DM	7(33.3%)	13(33.3%)	1.08	0.21-5.63	0.930
56.Hypertension	20(95.2%)	39(100%)	1.05	0.95-1.16	0.350
6.Smoking/ Tobacco	4(19%)	16(41%)	1.69	0.37-7.69	0.495

On follow up visits, the accretion of the number of the patients enrolled in the study accounted for majority of failed functional status of the secondary procedures. Out of 60 patients for the study, 39 patients reported a functional status of the fistula at six months of follow up. Death due to renal disease and its associated co morbid conditions is the main cause for loss to follow up. The primary patency of the AV access created at first follow up is around 81. 6 %(49/60) at first follow up. The assisted primary patency of the AV access at first follow up is around 83.3 %(59/60), contributed by the successful thrombectomy of the Brachiocephalic outlet thrombosis in the perioperative period.(Table 4)

4. DISCUSSION

Age and Gender:

Allon et al. found that female gender was the only independent predictor of decreased likelihood of fistula maturation. [4]In contrast, *Prischl et al*. found no significant differences in access survival between 80 men and 43 women on hemodialysis with first AVF [5].The different findings of these studies perhaps can be explained by the small sample sizes and the fact that the populations were derived from single center. In our present analysis, we found no relation between age, gender and primary or, secondary patency and primary failure rate. We found that gender has no impact on fistula survival, wherever the site of creation, a finding that was not matched with some recent reports indicating that women had poorer distal AVF survival.[6,7].This could be explained by the high incidence of manual works in our female patients. With regard to age and access patency several reports have failed to find any association between age and access complications[8,9,] although others reported a significant effect of age appearing after 6 months of follow-up.

Diabetes and Hypertension:

Garrancho and colleagues[10] have found higher incidence of fistula failure in patients with Diabetes Mellitus. According to *Field et al*, [11] Fistula survival rates in non-diabetics patients were higher than in patients with diabetes. However, this was not significant (p=0.11); (54, 48 and 34% in diabetics compared to 45, 35 and 26% in non-diabetics at 6, 12 and 24 months, respectively .In our study, we could not find statistical significant association between the Diabetes and the access dysfunction. (OR 0.83, C I=0.2-3.6). Out of 60 cases, 20 patients had diabetes (33. 3 %). 17 out of 20 cases had functional AV fistula. *Singh et al* [12] have stressed on securing a proximal AV fistula for improving the outcome in diabetic ESRD patients. In 15 out of 20 cases, we have created a proximal secondary vascular access; of which 11 are functional .This explains higher success rates in diabetic ESRD patients undergoing a proximal AV fistula. .The primary patencies of the access created are more than 6 months on follow up. *Gheith et al*[15] have found that hypertensive patients represented 76% of the study population, with nearly one-quarter of them receiving an Angiotensin converting enzyme inhibitor or Angiotensin Receptor blocker in addition to 2 other anti hyperertensive agents. Treatment with Angiotensin converting enzyme inhibitor or Angiotensin Receptor blocker or use of two or more antihypertensive drugs however was not a significantly influential factor in their study. In our study , 49 out of 50 patients had hypertension (98.0%) and is positively associated with the long term survival of the AV fistula (p value=0.057, table 35) .

Prior access Failure:

Tordoir et al [13]conducted a prospective study that has shown that the type of fistula, previous access surgery was significantly correlated to the development of poor flow and thrombosis (flow-related complications). *Dixon et al* [14] had favored upper arm AV fistulas for higher patency rates. The group had found higher one-, three- and five-year patency rates in upper arm fistulas (71%, 57% and 57%) compared to forearm AV fistulas (54%, 46% and 36%) and grafts (54%, 28%, 0%), but upper arm AV fistulas required more interventions than forearm AV fistulas (1.0 versus 0.6 per access, respectively).We have preferably conducted proximal elbow fistulas to yield more of functioning Arterio venous access. However, the number of prior access in the same limb could not gain statistical correlation with the functioning of the AV fistula. (P value =0.653)

Smoking:

Ozdemira et al[16] have concluded that when AVF location was excluded from the analysis, smoking (RR = 4.140, P < .01) and high blood eosinophil count (RR = 1.006, P < .005) were independent risk factors for thrombosis. *Wetzig et al*[17] have also confirmed that there was a significantly higher incidence of early and late fistula failure in those patients who were cigarette smokers. Our study also indicates that smoking count may contribute to the development of AVF thrombosis and hence the fistula failure (p value=0.023) and is associated with poor long term survival of the AV access. (P value 0.048)

Thrombotic complication of arterio venous access:

The treatment of thrombosed AV access is difficult, particularly in the setting of autogenous access thrombosis. In this case, the endothelial surface is significantly compromised, because thrombus rarely forms in native veins without some abnormality. Once thrombus develops, its removal usually leads to recurrent thrombosis because the underlying flow surface is abnormal. This is compounded by the trauma to the endothelial surface resulting from balloon thrombectomy. For this reason, surgical thrombectomy of failed autogenous access has limited value. *Palmer and colleagues*, presenting the largest series addressing this specific question, had technical success in 7 of 10 patients treated. However, the 6-month primary and secondary patency rates for technically successful cases were only 51% and 69%, respectively.[18,19,20]

Thrombosis, the main cause of AV fistula and/or graft dysfunction and failure, is usually the result of outflow tract obstruction. Stenosis is commonly thought to affect the access outflow tract, inflow stenosis is not uncommon in dysfunctional HD accesses and radiological evaluation should also include the arterial inflow.[21,22,23] Native AV fistulas are associated with two major problems: initial failure to mature (primary failure) and a later venous stenosis followed by thrombosis. Causative factors include a small artery (<1.5–2mm), a small vein (<2–2.5mm), poor surgical technique, hemodynamic stressors and a predisposition to vasoconstriction and neointimal hyperplasia. In terms of AV grafts, the etiological factors include haemodynamic stress at the graft–vein anastomosis, the type of graft material and injury owing to repeated needling. In predisposed AV access, thrombosis might be heralded by dehydration, hypotension, and compression during sleep and excessive pressure required to stop haemorrhage following dialysis.

In the present study, AV access thrombosis is the main cause of access dysfunction in 5 of 10 cases secondary procedures done for the failed AV fistulas. We have attempted surgical thrombectomy in 2 cases of recently failed fistuls with acceptable anatomy of the arteries and the veins, of which one could be salvaged. Since the number of cases of thrombectomy as a means of surgical salvage is very less, we could not compare with the available literature.

In a study conducted by *Osama Ashry Gheith* et al [24], optimization of hemoglobin levels between 10 g/dL and 12 g/dL is associated with longer fistula survival. Vascular access survived longer in less anemic patients than among severely anemic patients. However, no significant differences in VA survival among those with proximal fistulas. In another randomized controlled trial, Foley and coworkers [25] found no difference in the incidence of VA thrombosis in patients with low Hb (9.5 g/dL to 10.5 g/dL) compared to those with normal Hb levels (13.0 g/dL to 14.0 g/dL). In our present study, the mean hemoglobin was found to be 9.16±1.74 .The hemoglobin concentration of<8 gm% and the functioning of the AV access could not achieve statistical significance (p value 0.708) as we have mostly focused on creating a proximal AV fistula. [123]

Functional analysis of the secondary procedures:

Out of 60 secondary procedures, 50 remained patent at the 6months of follow up. Primary AV access thrombosis accounted for 5 of 10 the cases of failed secondary procedures .We had single case of access dysfunction due to uncontrollable infection and bleeding with resultant access abandonment .one case of CCF with closure of AV access, one case failed to mature. Poor vessel anatomy on exploration was evident in 7 cases; revision of the anastomosis was done in two cases, thrombectomy of the venous outflow was done in 2 cases, with salvage of a single AV access. *Pietro Ravani et al* [26]have shown similar results in their prospective study of 197 consecutive patients between 1995 and 2001.

To further illustrate the superior patency rates of autogenous access, *Huber and coworkers*[27] performed a meta-analysis of published literature from 1966 to 2001 and showed that primary patency rates for autogenous access were 72% at 6 months and 51% at 18 months; the corresponding rates for prosthetic AV access were 58% and 33%, respectively. Secondary patency rates for autogenous access were 86% at 6 months and 77% at 18 months, versus 75% and 55%, respectively, for prosthetic access.

A common tradeoff for the higher long-term patency rates of autogenous AV access is higher primary failure rates due to failure of access maturation or primary thrombosis. Initial success rates leading to a functional AV access range from 55% to 97%.

In our study, the primary patency of the procedures conducted for the management of the failed fistulas is 13.3%. The selection of the patients for a proximal AV fistula has given the distinct advantage of achieving higher success rate. We had two fully functional AV grafts ,but this number is too low for arriving at a conclusion .

Also of note, diabetes mellitus negatively affects both the maturation and the primary patency rates of autogenous AV access. *Hakaim and colleagues* [28] followed 58 consecutive patients with diabetes mellitus after initial autogenous AV access was placed and demonstrated a 70% non-maturation rate and a 33% primary patency rate for autogenous radial-cephalic wrist direct AV access, a 27% non-maturation rate and a 78% primary patency rate for autogenous brachial-basilic upper arm transposed AV access, and a 0% non-maturation rate and a 79% primary patency rate for autogenous brachial-cephalic upper arm direct AV access. Therefore, when selecting an AV access location in a patient with diabetes mellitus, the surgeon should consider upper arm autogenous AV access the primary choice. We have achieved primary patency of 73.3% in proximal AV fistulas created in diabetic failed AV access patients (11 out of 15 diabetic patients with functioning proximal AV fistulas).

5. CONCLUSION

Over the past few decades, hemodialysis and transplantation has prolonged the life of the patients of ESRD. Hemodialysis needs a good vascular access to receive the blood for dialysis and returning the blood back to the circulation. The concept of creating native AV fistula as early as possible is well accepted in the management of the patients requiring dialysis

We have found the following points for recommendation for improving the outcome form our study.

1. Preoperative duplex scan improves the outcome of the AV fistula.
2. Smoking is adversely associated with the fistula outcome.
3. Creating a proximal fistula is a rewarding option for patients with failed vascular access with an unfavorable arterio-venous anatomy in the duplex scan.
4. In diabetic patients, it is better to consider for a proximal ac fistula for better outcome.
5. We need to have more of comparative studies to opine regarding the smaller biometrics of the blood vessels in Indian patients, especially Asian population in comparison to the western world.

DECLARATIONS:

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Guarantor: Dr Sandeep Mahapatra is the guarantor for the Study.

Contributor ship: Dr Sandeep and Dr Pinjala Ramakrishna contributed for the literature search, Dr Sandeep had obtained the Ethical Committee Approval and Dr Anusha Arumalla prepared the draft for the manuscript.

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